

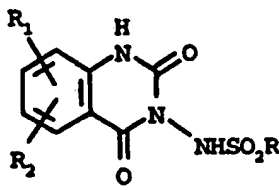
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<p>(21) International Application Number: PCT/EP95/00136 (22) International Filing Date: 13 January 1995 (13.01.95) (30) Priority Data: 9400680.6 14 January 1994 (14.01.94) GB (71) Applicant (for all designated States except AT DE US): SANDOZ LTD. [CH/CH]; Lichtstrasse 35, CH-4002 Basle (CH). (71) Applicant (for DE only): SANDOZ-PATENT-GMBH [DE/DE]; Lichtstrasse 35, CH-4002 Basle (CH). (71) Applicant (for AT only): SANDOZ-ERFINDUNGEN VERWALTUNGSGESELLSCHAFT M.B.H. [AT/AT]; Brunner Strasse 59, A-1230 Vienna (AT). (72) Inventor; and (75) Inventor/Applicant (for US only): KOLLER, Manuel [CH/CH]; Fuhrenstrasse 23, CH-3098 Schliern bei K�niz (CH). (74) Common Representative: SANDOZ LTD.; Patents and Trade-marks Div., Lichtstrasse 35, CH-4002 Basle (CH).</p>		<p>(81) Designated States: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, ES, FI, GB, GE, HU, JP, KE, KG, KP, KR, KZ, LK, LT, LU, LV, MD, MG, MN, MW, MX, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SI, SK, TJ, TT, UA, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, MW, SD, SZ). Published With international search report.</p>
<p>(54) Title: QUINAZOLINE-2,4-DIONES</p>		
<p>(57) Abstract</p> <p>Quinazoline-2,4-diones of formula (I) wherein R, R₁ and R₂ are as defined in the description, are useful as pharmaceuticals.</p> <div style="text-align: center;">  <p>(I)</p> </div>		

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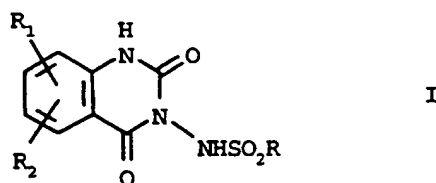
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QUINAZOLINE-2,4-DIONES

The present invention relates to quinazoline-2,4-diones, their production, their use as pharmaceuticals and pharmaceutical compositions containing them.

In particular the present invention provides compounds of formula I



wherein

R is (C₁₋₆)alkyl or phenyl optionally mono-, di- or trisubstituted by halogen, (C₁₋₄)alkyl, (C₁₋₄)alkoxy, nitro, trifluoromethyl, amino, (C₁₋₄)alkylamino, di(C₁₋₄)alkylamino, cyano, (C₁₋₄)alkylsulfonyl, phenylsulfonyl or sulfonylamino,

R₁ and R₂ independently are hydrogen, hydroxy, (C₁₋₄)alkyl, (C₁₋₄)alkoxy, (C₂₋₅)alkenyl, halogen, trifluoromethyl, nitro, amino, (C₁₋₄)alkylamino, benzyloxy, benzoylamino, carboxy, cyano, (C₁₋₄)alkoxy-carbonyl, (C₁₋₄)alkylsulfonyl, phenylsulfonyl, sulfonylamino, (C₂₋₅)alkanoylamino or phenyl optionally substituted by (C₁₋₄)alkyl, halogen or nitro, provided that R₁ and R₂ are not both hydrogen if R is unsubstituted phenyl, or

R₁ and R₂ on adjacent carbon atoms together form a group -CH=CH-CH=CH-, or a salt thereof.

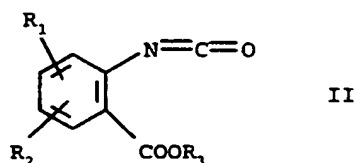
Alkyl and alkoxy groups and moieties in the compounds of formula I may be straight - or branched-chained. Halogen means fluorine, chlorine, bromine or iodine.

The compounds of formula I may form cationic salts, e.g. alkali metal or ammonium salts deriving from the sulfonamido group or when a carboxyl group is present. Depending on

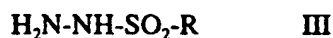
the nature of the substituents defined above, the compounds of formula I may also form acid addition salts. All these salts are part of the present invention.

The tautomeric forms of the compounds of formula I are also embraced by the invention.

The present invention also provides a process for the production of the compounds of formula I and their salts, which comprises reacting a compound of formula II



wherein R_1 and R_2 are as defined above and R_3 is (C_{1-4}) alkyl, with a compound of formula III



wherein R is as defined above, and, if desired, converting the obtained compound into a salt thereof.

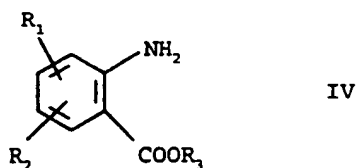
The process can be effected in conventional manner. The reaction can be carried out for example in the presence of a base, e.g. aqueous NaOH. The reaction is conveniently effected in a solvent, e.g. tetrahydrofuran.

For the preparation of compounds of formula I wherein R_1 and/or R_2 are hydroxy, amino or alkylamino, compounds of formula II wherein these groups are protected may be used. Deprotection is then performed after the cyclisation with the compounds of formula III, using conventional methods.

Working up of the reaction mixtures obtained according to the above processes and purification of the compounds of formula I thus obtained may be carried out in accordance to known procedures.

Cationic salts and acid addition salts may be produced in known manner from the free forms, and vice versa.

The compounds of formula II, used as starting material, can be prepared e.g. by reacting a compound of formula IV



wherein R₁, R₂ and R₃ are as defined above, with phosgen, using conventional methods.

The compounds of formula IV are known or may be produced from known compounds according to conventional processes.

The compounds of formula III are known or may be produced by reacting hydrazine with the appropriate sulfonylchloride.

In the following Examples, all temperatures are given in degrees centigrade and are uncorrected.

Example 1:**N-(7-chloro-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-yl)-methanesulfonamide**

To a solution of 0.55 g of methanesulfonyl hydrazide in 7 ml of THF, 1.06 g of methyl 4-chloro-2-isocyanato-benzoate in 7 ml of dry THF are added. The resulting suspension is stirred for 1 hour, then treated with 5 ml of 1N NaOH solution and stirred for 16 hours. After dilution with 5 ml of methanol and acidification with 3 ml of 2N HCl solution, the mixture is concentrated until formation of a precipitate, filtered and the residue washed with water, methanol and ether. Recrystallisation from THF gives the title compound, mp. 276-278°.

The starting material is obtained as follows:

A solution of 8 g of methyl 2-amino-4-chlorobenzoate in 80 ml of dry toluene is dropped at 17° into a mixture of 120 ml of phosgene (20% in toluene) and 35 ml of toluene. A slow stream of phosgene is introduced and the reaction mixture slowly heated to 120° (bath temp.) After 20 min. at this temperature, argon is blown through the solution and the solvent distilled off, thereby yielding the isocyanate as a yellow solid, sufficiently pure for the next step. IR (CHCl₃); 2250 cm⁻¹.

Example 2:

The following compounds are produced analogously to example 1:

- 2.1 N-(7-chloro-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-yl)-benzenesulfonamide, mp. 223-250°.
- 2.2 N-(7-chloro-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-yl)-2-nitrobenzenesulfonamide, mp. 303-309°.
- 2.3 N-(7-chloro-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-yl)-4-nitrobenzenesulfonamide, mp. >300°. MS (EI): m/e = 396 (M⁺).
- 2.4 N-(2,4-dioxo-1,4-dihydro-2H-benzo[g]quinazolin-3-yl)-methanesulfonamide,

mp. >280°. MS (FAB): m/e = 306 (MH⁺).

- 2.5 N-(7-chloro-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-yl)-4-methoxy-benzene-sulfonamide, mp. 275° (decomp.).
- 2.6 N-(7-fluoro-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-yl)-methanesulfonamide, mp. 263-265°.
- 2.7 N-(6,7-dimethoxy-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-yl)-methanesulfonamide, mp. >300°. MS (EI): m/e = 316 (MH⁺).
- 2.8 N-(7-nitro-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-yl)-methanesulfonamide, mp. 232-235°.
- 2.9 N-(5-chloro-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-yl)-methanesulfonamide, mp. 284-296°.
- 2.10 N-(7-methoxy-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-yl)-methanesulfonamide, mp. 256-265°(decomp.).
- 2.11 ethanesulfonic acid (7-chloro-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-yl)-amide, mp. 236-241°.
- 2.12 N-(7-bromo-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-yl)-methanesulfonamide, mp. 259-265°.
- 2.13 N-(6-chloro-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-yl)-methanesulfonamide, mp. 298-302°.
- 2.14 N-(2,4-dioxo-1,4-dihydro-2H-quinazolin-3-yl)-methanesulfonamide, mp. 260-262°.
- 2.15 N-(8-chloro-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-yl)-methanesulfonamide, mp. 270-274°.

- 2.16 N-(7-cyano-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-yl)-methanesulfonamide, mp. 280° (decomp.).
- 2.17 N-(6,7-dichloro-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-yl)-methanesulfonamide, mp. 280-286°.
- 2.18 N-(7-chloro-6-nitro-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-yl)-methanesulfonamide, mp. 284° (decomp.).
- 2.19 N-(7-tert-butyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-yl)-methanesulfonamide, mp. 234° (decomp.).
- 2.20 N-(2,4-dioxo-7-phenyl-1,4-dihydro-2H-quinazolin-3-yl)-methanesulfonamide, mp. 253° (decomp.).
- 2.21 N-(6-chloro-8-nitro-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-yl)-methanesulfonamide, mp. 256° (decomp.).
- 2.22 N-(7-methanesulfonyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-yl)methanesulfonamide, mp. 298-312°.
- 2.23 N-(2,4-dioxo-7-vinyl-1,4-dihydro-2H-quinazolin-3-yl)-methanesulfonamide, mp. 211-215° (decomp.).
- 2.24 N-[7-(2-ethyl-phenyl)-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-yl]-methanesulfonamide, mp. 279° (decomp.).
- 2.25 N-(7-fluoro-6-nitro-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-yl)-methanesulfonamide, mp. 233° (decomp.).
- 2.26 2-phenyl-ethenesulfonic acid (7-chloro-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-yl)-amide, mp. 277-284°.
- 2.27 N-(6,8-dichloro-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-yl)-methanesulfonamide, mp. 265-267° (decomp.).

- 2.28 N-(7-bromo-6-nitro-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-yl)-methanesulfonamide, mp. 287° (decomp.).
- 2.29 N-(5,7-dichloro-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-yl)-methanesulfonamide, mp. 268-271° (decomp.).
- 2.30 N-(6-benzyloxy-7-methoxy-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-yl)-methanesulfonamide, mp. (with 0.3 H₂O) 121-126° (decomp.).
- 2.31 N-(6-hydroxy-7-methoxy-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-yl)-methanesulfonamide, mp. 278-286° (decomp.).
- 2.32 N-(2,4-dioxo-7-trifluoromethyl-1,4-dihydro-2H-quinazolin-3-yl)-methanesulfonamide, mp. 232° (decomp.).
- 2.33 N-(7-ethyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-yl)-methanesulfonamide, mp. 250° (decomp.).

The compounds of formula I and their physiologically acceptable salts, hereinafter referred to as the active agents of the invention, exhibit pharmacological activity and are, therefore, useful as pharmaceuticals.

In particular the active agents of the invention exhibit an antagonistic activity at the kainic and 1-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) excitatory amino acid receptors. This can be demonstrated in standard tests, e.g. the inhibition of kainic acid resp. AMPA-induced depolarisations in rat brain slices ("wedges") according to N.L. Harrison et al., Brit. J. Pharmacol. 84 (1985) 381-391. The compounds are active in this test at concentrations of from about 0.01 µM/l to about 1mM/l. The compound of example 1 shows an inhibition of kainic acid induced depolarisations with a pA₂ of 5.7 and an inhibition of AMPA-induced depolarisations with a pA₂ of 5.6.

Furthermore the active agents of the invention exhibit a competitive antagonistic activity on the strychnine insensitive glycine site linked to the N-methyl-D-aspartate (NMDA) excitatory amino acid receptor. This can be demonstrated in standard tests.

In a binding assay based on methods according to Monahan et al., J. Neurochem. 53, 370-375 [1989] and White et al., J. Neurochem 53, 503-512 [1989], the active agents of the invention show affinity at concentrations of from about 0.01 to about 100 $\mu\text{M/l}$. In this test the compound of example 1 binds with a pK_i of 4.9.

In a functional test based on methods according to Reynolds et al., Proc. Natl. Acad. Sci. USA 84, 7744 (1987) and Wong et al., Eur. J. Pharmacol. 142, 487 (1987), the active agents of the invention inhibit the stimulating action of glycine on [^3H]MK-801 binding under non-equilibrium conditions at concentrations of about 0.01 $\mu\text{M/l}$ to about 1 mM/l . In this test the compound of example 1 shows an inhibition with a pA_2 of 4.9.

The active agents of the invention also show activity in in vivo tests.

For example the active agents of the invention show anticonvulsant activity in electroshock-induced convulsions in the mouse [E.A. Swinyard, J. Am. Pharm. Assoc. Scient. Ed. 38, 201 (1949) and J. Pharmacol. Exptl. Therap. 106, 319 (1952)]. In this test, the compounds are active on administration of about 0.5 to about 100 mg/kg i.p. The compound of example 1 has an ED_{50} of about 20 mg/kg i.p. and about 40 mg/kg p.o.

The active agents of the invention furthermore protect AMPA induced striatal lesions in rats on injection of about 10 to about 200 nM . This test is based on a method described by Massieu and Tapia, Neuroscience 59, 931 (1994). Injection of 50 nM of AMPA into the striatum causes excitotoxic damage which can be assessed by measurement of the remaining activity of the enzyme choline acetyltransferase (ChAT). With the compound of example 1, significant protection of ChAT-activity is obtained after co-injection of 60 nM together with 50 nM of AMPA.

Moreover the active agents of the invention at doses of about 1 to about 100 mg/kg p.o. inhibit amphetamine induced stereotypies, thereby indicating an antipsychotic profile (Snyder et al., Am. J. Psychiatry 130, 61 (1973)). The compound of example 1 reduces amphetamine induced rearing at doses from about 10 mg/kg p.o.

As a result of the above mentioned activities, the active agents of the invention are useful for the treatment of any pathology, disorder or clinical condition involving AMPA, kainate or NMDA receptors in their etiology, including epilepsy, high pressure neurological

syndrome, pain (e.g. cancer pain, arthritis), tinnitus, anxiety, spasticity, schizophrenia, depression, cognitive disorders, attentional deficit disorders, panic attack, sleep disorders, emesis, migraine, hormonal conditions (e.g. excess GH or LH secretion, corticosterone secretion in stress), intake of and tolerance and withdrawal symptoms produced by any addictive drug, e.g. ethanol, opiates or opiate-like drugs, barbiturates, amphetamine, and benzodiazepines, and cocaine.

Furthermore the active agents of the invention are useful in the treatment of any pathology, disorder or clinical condition involving AMPA-receptor mediated neuronal damage, i.e. neurodegenerative disorders (such as Huntington's, Alzheimer's or Parkinson's diseases, amyotrophic lateral sclerosis, supra nuclear palsy and olivoponto cerebellar atrophy), ischaemic and/or hypoxic conditions (for example stroke, subarachnoid haemorrhage, brain and spinal trauma, head injury, high intracranial pressure, and any surgical procedure potentially associated with hypoxia of the central nervous system, e.g. cardiac bypass, operations on extracranial vessels), and conditions produced by the actions of environmental, exogenous neurotoxins, including those produced by infection viruses (such as HIV, measles, rabies, tetanus), as well as those produced by metabolic changes (e.g. hypoglycaemia, non-ketotic hyperglycinaemia, sulphite oxidase deficiency and hepatic encephalopathy associated with liver failure).

For all these indications, the appropriate dosage will, of course, vary depending upon, for example, the compound of formula I employed, the host, the mode of administration and the nature and severity of the conditions being treated. However, in general, satisfactory results in animals are indicated to be obtained at daily dosages from about 0.1 to about 30 mg/kg animal body weight. In larger mammals, for example humans, an indicated daily dosage is in the range from about 5 mg to about 2 g of a compound of formula I conveniently administered, for example, in divided doses up to four times a day.

The active agents of the invention may be administered by any conventional route, in particular enterally, preferably orally, e.g. in the form of tablets or capsules, or parenterally, e.g. in the form of injectable solutions or suspensions.

In accordance with the foregoing, the present invention provides an active agent of the invention for use as a pharmaceutical, in particular for use in the treatment of any pathology, disorder or clinical condition involving AMPA, kainate or NMDA receptors in

their etiology or involving AMPA-receptor mediated neuronal damage, and especially for use in any of the specific indications hereinbefore recited.

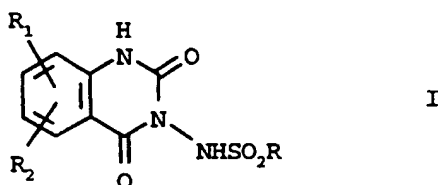
The present invention also provides a pharmaceutical composition comprising an active agent of the invention in association with at least one pharmaceutical carrier or diluent. Such compositions may be manufactured in conventional manner. Unit dosage forms contain, for example, from about 1 mg to about 400 mg of an active agent according to the invention.

The present invention furthermore provides the use of a compound according to the invention, for the manufacture of a medicament for the treatment of any pathology, disorder or clinical condition involving AMPA, kainate or NMDA receptors in their etiology or involving AMPA-receptor mediated neuronal damage.

Moreover the present invention provides a method for the treatment of any pathology, disorder or clinical condition involving AMPA, kainate or NMDA receptors in their etiology or involving AMPA-receptor mediated neuronal damage, in a subject in need of such treatment, which comprises administering to such subject a therapeutically effective amount of a compound according to the invention.

WHAT WE CLAIM IS:

1. A compound of formula I



wherein

R is (C₁₋₆)alkyl or phenyl optionally mono-, di- or trisubstituted by halogen, (C₁₋₄)alkyl, (C₁₋₄)alkoxy, nitro, trifluoromethyl, amino, (C₁₋₄)alkylamino, di(C₁₋₄)alkylamino, cyano, (C₁₋₄)alkylsulfonyl, phenylsulfonyl or sulfonylamino,

R₁ and R₂ independently are hydrogen, hydroxy, (C₁₋₄)alkyl, (C₁₋₄)alkoxy, (C₂₋₅)alkenyl, halogen, trifluoromethyl, nitro, amino, (C₁₋₄)alkylamino, benzyloxy, benzoylamino, carboxy, cyano, (C₁₋₄)alkoxy-carbonyl, (C₁₋₄)alkylsulfonyl, phenylsulfonyl, sulfonylamino, (C₂₋₅)alkanoylamino or phenyl optionally substituted by (C₁₋₄)alkyl, halogen or nitro, provided that R₁ and R₂ are not both hydrogen if R is unsubstituted phenyl, or

R₁ and R₂ on adjacent carbon atoms together form a group -CH=CH-CH=CH-, or a salt thereof.

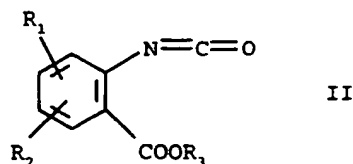
2. A compound selected from

N-(7-chloro-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-yl)-benzenesulfonamide,
 N-(7-chloro-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-yl)-2-nitrobenzenesulfonamide,
 N-(7-chloro-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-yl)-4-nitrobenzenesulfonamide,
 N-(2,4-dioxo-1,4-dihydro-2H-benz[g]quinazolin-3-yl)-methanesulfonamide,
 N-(7-chloro-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-yl)-4-methoxy-benzenesulfonamide,
 N-(7-fluoro-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-yl)-methanesulfonamide,
 N-(6,7-dimethoxy-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-yl)-methanesulfonamide,
 N-(7-nitro-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-yl)-methanesulfonamide,
 N-(5-chloro-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-yl)-methanesulfonamide,
 N-(7-methoxy-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-yl)-methanesulfonamide,

ethanesulfonic acid (7-chloro-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-yl)-amide,
 N-(7-bromo-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-yl)-methanesulfonamide,
 N-(6-chloro-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-yl)-methanesulfonamide,
 N-(2,4-dioxo-1,4-dihydro-2H-quinazolin-3-yl)-methanesulfonamide,
 N-(8-chloro-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-yl)-methanesulfonamide,
 N-(7-cyano-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-yl)-methanesulfonamide,
 N-(6,7-dichloro-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-yl)-methanesulfonamide,
 N-(7-chloro-6-nitro-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-yl)-methanesulfonamide,
 N-(7-tert-butyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-yl)-methanesulfonamide,
 N-(2,4-dioxo-7-phenyl-1,4-dihydro-2H-quinazolin-3-yl)-methanesulfonamide,
 N-(6-chloro-8-nitro-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-yl)-methanesulfonamide,
 N-(7-methanesulfonyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-yl)methane-
 sulfonamide,
 N-(2,4-dioxo-7-vinyl-1,4-dihydro-2H-quinazolin-3-yl)-methanesulfonamide,
 N-[7-(2-ethyl-phenyl)-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-yl]-methane-
 sulfonamide,
 N-(7-fluoro-6-nitro-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-yl)-methanesulfonamide,
 2-phenyl-ethenesulfonic acid (7-chloro-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-yl)-
 amide,
 N-(6,8-dichloro-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-yl)-methanesulfonamide,
 N-(7-bromo-6-nitro-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-yl)-methanesulfonamide,
 N-(5,7-dichloro-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-yl)-methanesulfonamide,
 N-(6-benzyloxy-7-methoxy-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-yl)-methane-
 sulfonamide,
 N-(6-hydroxy-7-methoxy-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-yl)-methane-
 sulfonamide,
 N-(2,4-dioxo-7-trifluoromethyl-1,4-dihydro-2H-quinazolin-3-yl)-methane-
 sulfonamide,
 N-(7-ethyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-yl)-methanesulfonamide,
 and their salts.

3. N-(7-chloro-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-yl)-methanesulfonamide or a salt thereof.
4. A process for the production of a compound of formula I as defined in claim 1 or

a salt thereof, which comprises reacting a compound of formula II



wherein R₁ and R₂ are as defined in claim 1 and R₃ is (C₁₋₄)alkyl, with a compound of formula III



wherein R is as defined in claim 1, and if desired, converting the obtained compound into a salt thereof.

5. A compound of formula I as defined in claim 1 or a physiologically acceptable salt thereof, for use as a pharmaceutical.
6. A compound of formula I as defined in claim 1 or a physiologically acceptable salt thereof, for use as a pharmaceutical in the treatment of any pathology, disorder or clinical condition involving AMPA, kainate or NMDA receptors in their etiology or involving AMPA-receptor mediated neuronal damage.
7. A pharmaceutical composition comprising a compound of formula I as defined in claim 1 or a physiologically acceptable salt thereof, together with a pharmaceutically acceptable carrier or diluent.
8. The use of a compound of formula I as defined in claim 1 or a physiologically acceptable salt thereof, for the manufacture of a medicament for the treatment of any pathology, disorder or clinical condition involving AMPA, kainate or NMDA receptors in their etiology or involving AMPA-receptor mediated neuronal damage.
9. A method for the treatment of any pathology, disorder or clinical condition involving AMPA, kainate or NMDA receptors in their etiology or involving AMPA-receptor mediated neuronal damage, in a subject in need of such treatment, which comprises

administering to such subject a therapeutically effective amount of a compound of formula I as defined in claim 1 or a physiologically acceptable salt thereof.

INTERNATIONAL SEARCH REPORT

Internat Application No
PCT/EP 95/00136

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D239/96

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	DE,B,10 68 263 (BAYER) 5 November 1959 see page 1 - page 2; claims; example 3 ---	1
A	CHEMICAL ABSTRACTS, vol. 79, no. 28, 1973, Columbus, Ohio, US; abstract no. 18752n, page 457 ;column 2 ; see abstract	1,5
A	& JP,A,7 301 674 (EISAI CO.) 19 January 1973 -----	1,5

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- * "A" document defining the general state of the art which is not considered to be of particular relevance
- * "E" earlier document but published on or after the international filing date
- * "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- * "O" document referring to an oral disclosure, use, exhibition or other means
- * "P" document published prior to the international filing date but later than the priority date claimed

- * "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- * "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- * "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- * "&" document member of the same patent family

Date of the actual completion of the international search

3 April 1995

Date of mailing of the international search report

- 5. 04. 95

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INTERNATIONAL SEARCH REPORT

Information on patent family members

Internat: Application No

PCT/EP 95/00136

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
DE-B-1068263		NONE	
JP-A-7301674		NONE	